

Available online on 30.08.2019 at <http://jddtonline.info>

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

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Review Article

Bridging Studies- A Key in the Extrapolation of Clinical Results between Regions

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ABSTRACT

In pharmaceutical industry, the sponsors are interested in bringing their drug products from one region (e.g., the United States of America) to another region (e.g., Asian Pacific) to increase the exclusivity of the drug products in the marketplace. However, it is about the clinical results that can be extended from the victim patient population in one region to a similar, but different patient population in a new region due to a possible difference in ethnic factors. The International Conference on Harmonization (ICH) suggested that a bridging study may be important to extrapolate the clinical results between regions. However, little or no information concerns the basis for determining whether a bridging study is necessary based on the assessment of the complete clinical data package provided by the ICH. Moreover no criteria on the evaluation of similarity of clinical results between regions is given.

Keywords: International Conference on Harmonization, Bridging study, Clinical trails

Article Info: Received 03 July 2019; Review Completed 14 Aug 2019; Accepted 20 Aug 2019; Available online 30 Aug 2019



Cite this article as:

Santosh Kumar R, Aditya Srinivas S, Bridging Studies- A Key in the Extrapolation of Clinical Results between Regions, Journal of Drug Delivery and Therapeutics. 2019; 9(4-A):751-753 <http://dx.doi.org/10.22270/jddt.v9i4-A.3480>

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INTRODUCTION

International development of pharmaceutical products has become the key to the favorable result of any pharmaceutical sponsors. It is therefore key to address the efficacy and safety difference of a new test pharmaceutical product among different geographic regions due to ethnic factors. For any marketing acceptance of pharmaceutical product in new region, sponsors are required to provide a considerable evidence of effectiveness and safety from sufficient and well controlled clinical trials. So, a bridging study is involved which is a supplementary study on a particular medicine that is performed in new region. Bridging studies mainly focuses on the effectiveness, safety and dose response of new drugs, that could provide an additional drug response data in the population of new region. However, after the pharmaceutical product is approved by the original region such as the united states or European union, sponsors might seek the registration of the product in the new region. Due to the possible differences on ethnicity and clinical practice of the new region, the concerns that these differences may have an impact on the safety, efficacy, dose, and dosing regimen that have limited willingness for the regulatory authority in the new region. Recently, geotherapeutics has attracted much attention from sponsors as well as

regulatory authorities from different geographic regions. To address this issue, the international conference on harmonization(ICH) has published a guideline is titled "Ethnic factors in the acceptability of foreign clinical data", which is known as ICH E5 guideline.

According to the ICH E5 guidance, ethnic factors are factors are associated with races or larger populations grouped according to common trails and customs which they mainly focus on pharmacodynamics and pharmacokinetic properties. Ethnic factors may be categorize intrinsic or extrinsic. Intrinsic ethnic factors are factors which include genetic polymorphism, age, height, gender, weight, lean body mass, body composition, and organ dis-function. Whereas extrinsic factors include social and cultural aspects of region, such as medical practices, diet, use of tobacco, use of alcohol and compliance with prescribed medications, particularly important are the reliance on studies from a different region, practices in clinical trials, design and conduct. A bridging study therefore can be done at the beginning, during or at the end of a global development programme. ICH E5 also contains a bridge data package of selected information from the complete clinical data package (CCDP), which is relevant to the population of the new region.

NATURE AND TYPES OF BRIDGING STUDIES

This guidance implemented when the regulatory authority of the new region is presented with a clinical data package to achieve its regulatory requirements, the authority should request only those additional data necessary to assess the ability to extend the foreign data from the Complete Clinical Data Package to the new region. The quality of the medicine to ethnic factors will help to control the amount of such data.

In most cases, a single trial that accomplished to provides these data in the new region and confirms the capability to extended data from the original region should enough and should not need further replication. Note that even though a single study should be sufficient to “bridge” efficacy data, a sponsor may find it practical to obtain the necessary data by managing more than one study. From the ICH E5 guidance the following table explains the types of bridging studies by controlled clinical trials (Table 1).

Table :1 Controlled clinical trails

Medicine	Region	Medical practices	Drug class	Clinical experience	Bridging studies
Insensitive	-	Similar	-	-	No
Sensitive	Similar	-	-	Sufficient	No
Sensitive	Dissimilar	Similar	Familiar	-	No
Dosage	-	Different	Unfamiliar	Insufficient	CCDP

The population between two regions are similar and their clinical trials are also similar and medical trails are done equally for both regions and the variation between two regions are shown in the table 1. If the medicine is insensitive and medical practices are similar in both the regions and the drug class is familiar one in the region, then it is controlled pharmacodynamic (PD) study with a well established pharmacological end point may generate the necessary data to bridge the foreign clinical data. However the medicine is sensitive and it is done in similar regions with sufficient clinical experience without any study of bridging studies, then it is controlled by a pharmacokinetic (PK), the general relationship between PK, PK/PD and clinical studies are indefinite. The similarity observed from PK studies to reproducibility in clinical trials requires further research. The type of research can start by examining systematically the relationship among PK, PD, and clinical data of approved drugs by drug class.

Extrapolation and similarities:

ICH E5 clearly states that assessment of ability to extrapolate foreign data depends upon similarity of dose response efficacy & safety between new and original regions. The treatment effect for region is defined as

$$(\Delta_{1-\mu T-\mu 1p1} \quad I=0_{1\mu})$$

Let Y_{jk} be some efficacy response variable for patient k receiving treatment j in region I , $k=1, \dots, k; j=T(\text{test}), p$ $I=0(\text{original})$ $N(\text{new})$.

The concept of positive treatment effect is defined as the medicine has already been approved in original region due to its efficacy placebo control in some new region data is collected from bridging studies. The new region demonstrate superior efficacy test medicine over test medicine over placebo control the effect from similarity can be educated through the following hypothesis.

$$H_0=\Delta_N \leq 0 \text{ vs } H_a:\Delta_N > 0 \dots (1)$$

The positive treatment effect does not really gives the similarity of the magnitude of efficacy between two regions bio equivalence to evaluation of similarity of extrapolation of foreign clinical data relationship between δ and overall treatment effect Δ can be expressed as $\delta=f\Delta$, δ is clinically

acceptable and meaningful only if $0 < f < 1$ because similarity dictates that the difference of treatment effect.

Let $\Theta = (\mu_{NT} - \mu_{NP}) - (\mu_{OT} - \mu_{OP})$ the corresponding hypothesis can be formulate as following two sided equivalence hypothesis.

$$[H_0 = \Theta \leq -\delta \text{ or } \Theta \geq \delta \text{ vs } H_a: -\delta < \Theta < \delta] \dots (2)$$

The non-linearity test may also appropriate for evaluation of the difference between two regions that are evaluated the one region has similar it and the new region doesn't have any similarity in efficacy. The one sided non inferiority hypothesis is given as.

$$[H_a: \Theta \leq -\delta \text{ vs } H_0: \Theta \geq -\delta] \dots (3)$$

ShiH proposed the idea of consistency for evaluation of the similarity of the efficacy between the new and original region, Let $w = (w_1, \dots, w_N)$ be the result of the H reference studies that were conducted in the original region and let v be the result of the bridging study is said to be constant with the previous result w if

$$P(v/w) \geq \min \{p(w_n/w) \mid n=1, \dots, H\} \dots (4)$$

When $P(u/w)$ is the productive probability function of the study U given the previous result W the concept of consistency in eq :4 can be reformulated.

$$|\Delta_N - \Delta| < V \dots (5)$$

Where Δ is the mean of treatment effect over the H previous studies under the normal assumption.

$$V^2 = \max [(\Delta_h - \Delta_1)^2 \mid h=1, \dots, H]$$

CONCLUSION

For the pharmaceutical product before being marketed need to be evaluated for means of product safety efficacy and potency by the guidance of various regulatory bodies and other guidelines for performing clinical trials to determine & ensure the product. The ICH E5 guidelines provides information regarding clinical trials and the acceptance criteria for the pharmaceutical product like safety efficacy and quality this intern follows various evaluation and analytical methods that describes the product properties and its acceptance into the market during the investigational studies of pharmaceutical products.

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